REMARKS

The Official Action dated September 26, 2007 and references cited therein have been carefully reviewed. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are requested.

Status of the prosecution.

This is a non-final Office Action following Applicant's filing of a response and Request for Continued Examination, and a supplemental response following an examiner interview. Claims 163-180 are pending and were examined.

Claims 163-180 were rejected under 35 U.S.C. §112, first paragraph, on the ground that the amendment to claim 163 to recite "up to about 30% by weight" allegedly has introduced new matter.

Claims 163-180 remain rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-34 of U.S. Patent 7,045,145. The Action acknowledged Applicant's intention to file a terminal disclaimer upon determination of allowable subject matter.

Claims 163-166 and 171-180 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. 5,762,956 (the 956 patent) in view of U.S. 5,023,084 (the 084 patent).

Claims 167-170 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the 956 patent in view of the 084 patent, and in view of U.S. 6,007,835 (the 835 patent).

Current amendments to the specification and/or claims.

Claims 163 has been amended and new claims 181 and 182, which depend from claim 163, have been added. Claim 163 has been amended to delete the recitation "up to 30% by weight," and to add the limitation "wherein the capric acid is present in an amount between about 3% and about 9% by weight of the adhesive polymer matrix." Dependent claims 181 and 182 recite more specific limitations to the amount of capric acid in the adhesive polymer matrix. Support for these claim amendments and new claims may be found throughout the specification, e.g., at paragraphs 0015 and 0066, among others.

No new matter has been added by way of the claim amendments. For the reasons set forth below, Applicant submits that the claims are in condition for allowance.

The claims satisfy all requirements of 35 U.S.C. §112, first paragraph.

Claims 163-180 were rejected under 35 U.S.C. §112, first paragraph, on the ground that the amendment to claim 163 to recite "up to about 30% by weight" allegedly has introduced new matter. Without conceding to the correctness of this allegation, and in order to advance prosecution of the claims to allowance, the term "up to about 30% by weight" has been deleted from claim 163. Accordingly, the rejection on this ground should be moot. Reconsideration and withdrawal of the rejection is therefore requested.

The non-statutory obviousness-type double patenting rejection can be overcome.

All claims remain rejected on the grounds of nonstatutory double patenting as allegedly unpatentable over claims 1-34 of U.S. Patent 7,045,145. Applicant reiterates his intention to file a terminal disclaimer upon determination of allowable subject matter.

The claimed subject matter is not obvious in view of the cited prior art.

Claims 163-166 and 171-180 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. 5,762,956 (the 956 patent) in view of U.S. 5,023,084 (the 084 patent). According to the Office Action, the 956 patent teaches a transdermal hormone delivery system of the type presently claimed, but comprising a combination of three skin permeation enhancers comprising dimethyl sulfoxide, lauryl lactate and ethyl lactate. The Action acknowledges that the 956 patent does not teach capric acid in the mixture of skin permeation enhancers. The Action alleges, however, that the 084 patent teaches a transdermal estrogen/progesterone dosage unit comprising an adhesive matrix with permeation enhancers, wherein capric acid is a preferred enhancing agent because it provides "highly satisfactory skin absorption enhancement." The Action states that the 084 patent teaches capric acid in an amount as low as 10%. The Office Action alleges that, for these reasons, the skilled artisan would have been motivated to modify the three-enhancer-containing transdermal delivery device taught by the 956 patent by the addition of capric acid as a fourth skin permeation enhancer, in an amount as low as 10%, with a reasonable expectation of having a transdermal delivery device with highly satisfactory skin absorption enhancement for the combination of estrogen and progesterone. Applicant continues to traverse this rejection.

First, as pointed out previously, the 956 patent teaches away from adding anything to the enhancer combination disclosed therein. Through its repeated use of the term "consisting

of," and "unique combination," the 956 patent teaches that its three enhancer system is not amenable to alteration or supplementation.

In contrast, the transdermal delivery system of the present invention specifies a combination of four skin permeation enhancers, clearly taught against by the 956 patent, wherein capric acid in an amount of 3-9% by weight of the adhesive polymer matrix, is added to the enhancer combination. The teachings of the 956 patent provide no suggestion to modify the system disclosed therein to arrive at that invention.

The 084 patent does not supply the requisite teachings that are absent from the 956 patent, and indeed teaches away from the use of capric acid in the low amount currently specified in the amended claims . As the Office Action acknowledges, the 084 patent teaches capric acid as a preferred skin permeation enhancer for certain progestins and estrogens, in an amount as low as 10%, with preferred ranges being 15-30% (w/w) to achieve the "highly satisfactory skin absorption enhancement and satisfactory adhesion" (col. 17, lines 53-57). The Office Action states that it would have been obvious to the skilled artisan to add as low as 10% of capric acid to the 956 patent's system, in view of those teachings of the 084 patent. Even assuming for the sake of argument that this is true (and Applicant does not concede the point), there is nothing in the 084 patent to suggest to the skilled artisan that addition of *less than* 10% of capric acid would be a useful modification to the 956 patent's system. And indeed, by specifying a range of 10-40% and a preferred range of 15-30%, addition of less than 10% of capric acid is taught away from by the 084 patent.

Hence, there is no rational basis taken from either the 084 or the 956 patent, or the combination of those teachings, to impart to the skilled artisan any reason for adding 3-9% by weight of capric acid to the system of the 956 patent, to produce the presently claimed transdermal delivery system. Accordingly, the presently claimed system cannot be said to be obvious in view of the teachings of those two patents.

For the reasons set forth above, the presently claimed invention cannot be said to be obvious in view of the cited references. The rejections under 35 U.S.C. §103(a) should therefore be withdrawn for these reasons alone. But Applicant reminds the Office that rebuttal evidence of non-obviousness of the present invention has also been made of record, and should be reviewed in reconsidering the presently amended claims. As stated in the Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (Federal Register Vol. 72,

No. 195, October 10, 2007, 57526, 57535), "[O]nce the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record (citation omitted). All the rejections of record and proposed rejections and their bases should be reviewed to confirm their continued viability." In the present circumstances, the claim amendments submitted herewith necessitate reconsideration of the rebuttal evidence of record.

For the examiner's convenience Applicant is attaching copies of the previously-submitted evidence of non-obviousness, namely, (1) the Declaration of Agis Kydonieus, Ph.D. (without cited references), and (2) the Declaration of Thomas M. Rossi, Ph.D.

As discussed previously, the Declaration of Dr. Kydonieus sets forth a detailed explanation as to why the transdermal system claimed in the present application is not obvious in view of the cited references. First, as detailed in Paragraphs 9-17, the field of transdermal drug delivery is not predictable. Dr. Kydonieus sets forth a detailed explanation as to why this is the case, even when enhancers are not used (Kydonieus Decl. ¶¶10-13). When chemical enhancers are employed, the complexity and unpredictability of transdermal systems increases because they behave substantially differently when co-delivered with other enhancers and with the drugs themselves (Kydonieus Decl. ¶¶14-16). For these reasons, the effect of enhancers on the skin permeation of drugs is unpredictable and dependent on many variables whose effect can only be determined by experimentation (Kydonieus Decl., ¶17).

Second, as detailed in Paragraphs 18-20, Dr. Kydonieus believes that the unpredictability in the art would have made it impossible for the skilled artisan to arrive at the presently claimed formulation from the information provided in the 956 and 084 patents. Dr. Kydonieus points out that the system of the 956 patent was deficient in part because of insufficient delivery of progestin hormone to the bloodstream, and that the present invention overcomes this deficiency by making a modification to the enhancer system, namely, by adding a small amount of capric acid (Kydonieus Decl., ¶18). Dr. Kydonieus explains in detail why the 084 patent's information was completely insufficient to provide the skilled artisan with any guidance as to how to improve on the system of the 956 patent in the manner claimed in the present application (Kydonieus Decl., ¶19). He concludes that the presently claimed specific modifications of the 956 patent's system could not have been imparted in any way to the skilled artisan by the teachings of the 084 patent, and that significant trial-and-

error experimentation was likely the means by which the inventor settled upon the claimed modifications (Kydonieus Decl., ¶20).

Third, the Declaration of Dr. Kydonieus goes on to provide a further rationale for finding the claimed invention non-obvious over the cited references. Namely, as detailed in Paragraphs 21 and 22, Dr. Kydonieus notes the comparative *in vitro* and *in vivo* data presented by the 956 patent and the present application and its parent (Kydonieus Decl., ¶21). He points out that the *in vitro* skin flux results with the capric-acid containing patch of the present invention were actually poorer than that of the 956 patent's transdermal system, yet in the clinical studies, the steady state serum concentration of progestin delivered by the present invention's system was several-fold better than that delivered by the same size patch of the 956 patent's system (Kydonieus Decl., ¶22). Dr. Kydonieus is of the opinion that this many-fold improvement in *in vivo* progestin delivery by re-formulating the matrix to include a small amount of capric acid was not expected, and could not have been predicted from the information presented in the 956 patent or the 084 patent.

The Declaration of Thomas R. Rossi sets forth yet additional evidence of non-obviousness of the present invention, specifically, evidence of commercial success. Dr. Rossi currently serves as President and Chief Executive Office of Agile Therapeutics, Inc., licensee and developer of the technology disclosed and claimed in the present application (Rossi Decl., ¶6). Dr. Rossi also notes the excellent *in vivo* results afforded by a transdermal delivery system of the present invention, as compared with that of the 956 patent, and that such results could not have been predicted from the information taught in the cited references (Rossi Decl., ¶8). Dr. Rossi attests that the robust delivery of progestin afforded by the system of the present invention, but lacking in the 956 patent's system, was the impetus for Agile Therapeutics to license the technology and to invest in development of a commercial product (Rossi Decl., ¶9). Dr. Rossi elaborates that Agile Therapeutics and its predecessor have raised a total of $31.5 million dedicated to product development activities based on the invention of the present application. He notes that these investments were made by high quality private equity investors with experience in health care product development and commercialization (Rossi Decl., ¶10). Clearly, the commercial success of the technology covered by the claimed invention, as attested to by Dr. Rossi in his Declaration, must be taken as further compelling evidence of the non-obviousness of the present invention over the cited prior art.

In a previous Action, the Office discounted the aforementioned evidence of non-obviousness on the ground that it was not commensurate with the scope of the invention as claimed. Applicant urges reconsideration of this evidence in light of the current claim amendments, resulting in a claim scope that is clearly commensurate with the exemplified compositions referred to in the comparative data and the statements of commercial success.

Claims 167-170 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the 956 patent in view of the 084 patent, and further in view of U.S. 6,007,835 (the 835 patent). Applicant continues to traverse this rejection. The addition of the 835 patent to support the rejection of claims 167-170 is also untenable in view of the absence of teaching in the 956 patent and the 084 patent of the invention as currently claimed. The 835 patent's purported teaching of PVP/VA-S30 do not supply a reason to combine the teachings of the cited references so notably absent from the primary references.

In summary, Applicant has presented reasoning and evidence to support his assertion that the invention as presently claimed is not obvious over the cited references. Applicant therefore requests reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

Conclusion.

In view of the amendments submitted herewith, the evidence re-submitted herewith and the foregoing remarks, the presently pending claims are believed to be in condition for allowance. Applicant respectfully requests early and favorable reconsideration and withdrawal of the rejections set forth in the September 26, 2007 Official Action, and allowance of this application.

Respectfully submitted,

Date: October 29, 2007

Janet E. Reed, Ph.D.
Registration No. 36,252

Drinker Biddle & Reath, LLP
One Logan Square
18th and Cherry Streets
Philadelphia PA 19103
Telephone: (215) 988-3338
Facsimile: (215) 988-2757